II. Remarks

A. Status of the Claims

Claims 15, 20-23 and 25-29 will be pending after entry of this amendment. Claims 1-14, 16-19 and 24 were previously cancelled. Claims 15, 25 and 26 have been amended without prejudice. New claims 27-29 have been added. Applicants respectfully submit that no new matter has been added by virtue of this amendment.

B. Claim Rejections Under 35 U.S.C. § 103(a) over Malterud et al., Manthey et al. and Bok et al.

In the Office Action, claims 15, 20-23 and 25-26 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Malterud et al. ("Inhibitors of 15-lipoxygenase from orange peel", *J. Agric. Food Chem* (2000 Nov); 48(11): 5576-80, Abstract) and U.S. Patent No. 6,184,246 to Manthey et al. in view of U.S. Patent No. 6,096,364 to Bok et al.

1. Independent Claim 15

Prior to addressing this rejection as it applies to independent claim 15, Applicants respectfully point out that claim 15 has been amended to recite "administering an effective amount of a polymethoxyflavone composition comprising an effective ratio of sinesetin, nobiletin, tangeretin, heptamethoxyflavone and tetramethylscutellarein."

This rejection is respectfully traversed. Applicants submit that the Malterud and Manthey references, in view of the Bok reference, do not provide motivation to one of skill in the art to administering an effective amount of a polymethoxyflavone composition comprising an effective ratio of sinesetin, nobiletin, tangeretin, heptamethoxyflavone and tetramethylscutellarein to reduce serum insulin levels by at least about 26%, as recited by independent claim 15 and the claims depending therefrom.

Contrary to the Examiner's statement that "the five disclosed polymethoxylated flavones are taught as a group comprising thereof for inhibition of 15-lipoxygenase", Applicants submit that the Malterud reference does not list only the five claimed polymethoxylated flavones, but rather recites a list of virtually every element found in orange peel, i.e., hexamethoxyflavone, sinensetin, nobiletin, tangeretin,

tetramethylscutellarin, heptamethoxyflavone, hesperidin and ferulic acid. Therefore, Applicants submit that the Malterud reference does not provide motivation to use an effective ratio of the five specifically claimed polymethoxyflavones to reduce serum insulin levels by 26%. Further, as admitted by the Examiner, the Manthey and Bok references do not teach on tetramethylscutellarein, one of five polymethoxyflavones recited in claim 15.

Additionally, Applicants re-submit that the Manthey, Malterud and Bok references are improperly combinable. As discussed in Applicants' previous response, the Manthey reference is directed to "a method of inhibiting the production of cytokines" which associated diseases include "septic shock, cancer, cachexia, chronic rheumatism, ulcerative colitis, Crohn's disease…". Manthey et al. at Abstract and Col. 2, lines 58-59. The Malterud and Bok references are directed to inhibition of 15-lipoxygenase and glucose reduction, respectively. Therefore, Applicants submit that one of skill in the art would not combine the Manthey reference with the Malterud and Bok references, as they are directed to different fields of endeavor.

In response to Applicants' previous argument regarding the improper combinability of these references, the Examiner quotes a passage from Natarajan et al. which describes a relationship between cytokines and inflammation, which is purportedly associated with diabetic vascular disease. Applicants wish to respectfully point out that the Natarajan reference was published in 2004, which is after the filing date of the present application, and therefore does not evidence that it was known at the time of filing of the present application that the inhibition of cytokines may be somehow related to diabetic vascular disease. In any event, Applicants submit that this purported relationship still does not provide the motivation to combine the cited references. The Manthey reference lists the disease it claims are associated with the polymethoxyflavone composition described therein, and diabetes is not one of the listed disease states. Therefore, Applicants submit that one of skill in the art would not be motivated to combine the Manthey reference with the Malterud and Bok references.

Further, Applicants point out that the Bok reference is directed to a method of lowering blood glucose levels in a mammal by administering hesperetin, naringenin or rutin. See Bok, generally. Applicants respectfully point out that hesperetin, naringenin

and rutin are not polymethoxyflavones. See, e.g., Bok et Col, 3, Table II and the present specification at paragraph [0028-0029] which show that hesperetin, naringenin and rutin fail to meet the definition of a polymethoxylfavone, i.e., "flavones substituted with two or more methoxy groups." Thus, Applicants submit that the Bok reference is improperly combinable with the Malterud and Manthey references, as it is not directed to polymethoxyflavones.

Even assuming arguendo that the references were properly combinable, Applicants submit that the Bok reference fails to cure the deficiencies of the Malterud and Manthey references. The Examiner relies upon the Bok reference because it purportedly "teach a method for lowering blood glucose levels in diabetic patients by administration of bioflavonoid" and that "the polymethoxylated flavones taught are nobiletin, sinensetin, and tangeretin (col 1, Table 1 [Bok])". However, as discussed *supra*, Applicants point out that the Bok reference does not teach a method for lowering blood glucose levels in diabetic patients by administration of polymethoxylated flavones, but rather only teaches the use of bioflavonoids which are not polymethoxyflavones. Nobiletin, sinensetin, and tangeretin are only mentioned in a laundry list of bioflavonoids found in citrus fruits in Table 1 of the Bok reference. Therefore, Applicants submit that the Bok reference does not teach a method of lowering blood glucose levels in diabetic patient by administration of polymethoxyflavones, as alleged by the Examiner.

2. Independent Claim 26 and 27

Prior to addressing this rejection as it applies to independent claim 26 and new claim 27, Applicants point out that claim 26 has been amended to recite that the composition used in the claimed method "consist[s] essentially of an effective amount of a polymethoxyflavone composition consisting of nobiletin and tangeretin." Applicants also point out that new claim 27 recites a method which uses "a solid or liquid composition comprising an effective amount of a polymethoxyflavone composition consisting of nobiletin and tangeretin, wherein the polymethoxyflavone composition does not comprise any other polymethoxyflavones".

In making the rejection to claim 26, the Examiner states that the phrase "consisting essentially of nobiletin and tangeretin...still suggests or supports nothing to the exclusion of other said PMF's" and that 'the overall composition itself is still open to the inclusion of additional elements due to the use of 'comprising' in the description of the solid or liquid composition."

In response, Applicants respectfully submit that the amendments made to claim 26, and the limitations of new claim 27, exclude any polymethoxyflavones other than nobiletin and tangeretin from the composition.

Applicants further submit that, in view of the Malterud and Manthey references, one of skill in the art would not be motivated to administer an effective amount of a polymethoxyflavone composition which contains only nobiletin and tangeretin, to reduce serum insulin levels by at least about 26%, as recited by independent claims 26 and 27.

As discussed *supra*, the Malterud reference recites a list of virtually every element found in orange peel, i.e., hexamethoxyflavone, sinensetin, nobiletin, tangeretin, tetramethylscutellarin, heptamethoxyflavone, hesperidin and ferulic acid. Therefore, Applicants submit that the Malterud reference does not provide motivation to use an effective amount of the two specifically claimed polymethoxyflavones to reduce serum insulin levels by 26%.

Additionally, as discussed *supra*, it is Applicants position that the Manthey, Malterud and Bok references are improperly combinable, as they are directed to different fields of endeavor.

Further, as discussed *supra*, even assuming the references were properly combinable, Applicants submit that the Bok reference fails to cure the deficiencies of the Malterud and Manthey references, as the Bok reference only teaches a method of lowering blood glucose levels in diabetic patient by administration of bioflavonoids which are not polymethoxyflavones.

Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) over the Malterud and Manthey references in view of the Bok reference be removed.

C. Claim Rejection Under 35 U.S.C. § 103(a) over Malterud et al., Manthey et al. and Bok et al. further in view of Pershadsingh and Robbins

In the Office Action, the Examiner rejected claim 25 under 35 U.S.C. § 103(a) as being unpatentable over the Malterud, Manthey and Bok references as applied to claims 15 and 20-23, further in view of U.S. Patent No. 6,087,385 to Pershadsingh et al. and U.S. Patent No. 3,867,541 to Robbins.

This rejection is respectfully traversed. In addition to the reasons set forth *supra* with respect to the Malterud, Manthey and Bok references, Applicants submit that the combination of these references with the Pershadsingh and Robbins references fail to provide the motivation for one of skill in the art to treat a mammal having metabolic abnormalities resulting from insulin resistance by administering an effective amount of a polymethoxyflavone comprising an effective ratio of about 9.3% sinesetin, about 35% nobiletin, about 11.1% tangeretin, about 33.5% heptamethoxyflavone and about 11.1% tetramethylscutellarein, as recited in claim 25.

As stated by the Examiner, Pershadsingh "does not teach tangeretin or any other agents in its class as a single or combination therapy for insulin resistance." The Examiner also stated that the instant specification "fails to disclose the reason for specificity in percentages of disclosed polymethoxyflavones".

Applicants respectfully point out that the instant specification at paragraphs [0054-0064] exemplifies a formulation used in in-vivo studies comprising the specifically claimed percentages of combination of polymethoxyflavones. A 1% dietary supplement with the formulation having the claimed percentages of polymethoxyflavones was compared with a 1% dietary supplement of a single polymethoxyflavone, i.e., tangeretin. The comparative data can be seen in Table 2 for the single polymethoxyflavone composition, and Tables 4 and 5 for the claimed combination polymethoxyflavone composition. For the Examiner's convenience, pertinent portions of the Tables have been recreated below:

Diet	% change of serum insulin
Control[1]	-7%
+1.0 % Tangeretin	-20%
+1.0 % PMF (combination of claim 25)	-26%

In view of this data, Applicants submit that the claimed combination polymethoxyflavone composition resulted in a greater reduction of serum insulin as compared to an equal dosage of a single polymethoxyflavone composition, thereby demonstrating the reason for specificity in percentages of the disclosed polymethoxyflavones, pursuant to the Examiner's request.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the Malterud, Manthey and Bok references in view of the Pershadsingh and Robbins references be removed.

[1] Data for control taken from Table 5, paragraph [0084] of Specification

III. Conclusion

In view of the amendments made and arguments presented, it is believed that all claims are in condition for allowance. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is invited to telephone the undersigned at (973)597-6162. The undersigned also may be contacted via e-mail at epietrowski@lowenstein.com. All correspondence should be directed to our address listed below.

AUTHORIZATION

The Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment, to Deposit Account No. 50-1358.

Respectfully submitted,
Lowenstein Sandler PC

Date: February 19, 2008

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